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Hidden Fungi as Microbial and Nano-Factories for Anticancer Agents

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Plant hidden fungi (endophytic fungi) are defined as the fungi which live the whole or part of their lifecycle inhabiting intra -and/or inter-cellularly inside the healthy plants, naturally causing no apparent symptoms of disease [1]. Plant endophytic fungi are a significant and unique source of natural bioactive composites with their possible applications in medicine and food industry, agriculture. Certainly, since the discovery that the endophytic fungi associated form *Taxusbrevifolia*, *T. celebica*, *T. mairei*, *T. chinensis* var. *mairei*, and *T. wallachiana* produced the anti-tumor drug taxol (paclitaxel), many mycologist have recorded the endophytic fungi of herbal plants to identify potential sources of novel remedy [2-4]

Nineteen endophytic fungal genera (i.e. *Aspergillus, Alternaria, Botrytis, Botryodiplodia, Cladosporium, Ectostroma, Fusarium, Mucor, Monochaetia, Metarhizium, Ozonium, Papulaspora, Periconia, Pestalotiopsis, Pestalotia, Pithomyces, Phyllosticta, Taxomyces, Tubercularia*) were screened to produce paclitaxel and its analogues (i.e. baccatin III, 10-deacetyl baccatin III). The plant hosts of paclitaxel-producing fungi mainly include Taxus (i.e. *T. baccata, T. cuspidata, T. media*, and *T. yunnanensis*) and non-Taxus species (i.e. *Citrus medica*, *Cardiospermumhelicacabum*, *Cupressus* sp., *Hibiscus rosa-sinensis*, *Ginkgo biloba*, *Podocarpus* sp., *Taxodiumdistichum*, *Terminaliaarjuna, Torreyagrandifolia*, and *Wollemianobilis*) [5].

Paclitaxel is one of the best known and most curious examples of anticancer medication derived from endophytic fungi [6-7].Paclitaxel is one of the most commonly used anti-tumor remedies eternally developed and is active against a wide range of human cancers, such as breast, lung, and ovarian cancers, however it demonstrates poor water solubility, which results in the difficulty challenging the development of paclitaxel parenteral formulations, so its medical application is seriously limited [8]. A series of novel formulations of paclitaxel based on nanotechnology have been developed, including albumin-bound paclitaxel, polymeric micelle-formulated paclitaxel, polymer-paclitaxel conjugates, liposome encapsulated paclitaxel etc. [8]. These nanoformulations can significantly decrease toxicity of paclitaxel and significantly promote its anticancer efficacy [9].

The endophytic fungus *Trametes hirsute*, is able to produce podophyllotoxin from *Podophyllum hexandrum* and other linked aryl tetralinlignans with effective anticancer properties [10]. Podophyllotoxin and analogs are clinically important compounds due to their anticancer and antiviral activities [11-12]. Presently, novel fungal sources of Podophyllotoxin were reported from the endophytic fungi *Aspergillus fumigates* collocted from *Juniperus communis* [11], *Phialocephala fortinii* isolated from *Podophyllum peltatum* [13], and *Fusarium oxysporum* from *Juniperus recurva*[12]. Nanoformulation of podophyllotoxin suitable for controlled release drug delivery, podophyllotoxin-loaded solid lipid nanoparticles (PPT-SLNs) were developed, characterized and observed for *in vitro* cytotoxicity and to inhibit cancer progression [14].

The antitumor properties of the entophytic fungi products Camptothecin, 9-methoxycamptothecin and 10-hydroxycamptothecin were previously described. The products were obtained from entophytic *Fusarium solani* associated with *Camptotheca acuminate* [11]. Some reports have described other Camptothecin and two analogues producing endophytes [15]. Hot high-pressure homogenization protocol was used to prepare camptothecin (CA) combined into solid lipid nanoparticles (SLNs) [16].

Phaeosphoramides A and B, two new carbon skeleton derivatives, were isolated from the endophytic fungus *Phaeosphaeriaavenari*. Phaeosphoramide A was found to be an inhibitor of the signal transducer and activator of transcription (STAT)-3, which plays an important role in regulating cell growth and persistence, constitutea majoranticancer therapeutic [17].

There is agroup of substances known asthe cytochalasins, thesedrugs have antitumor activity, but they also have cellular toxicity was produced by *Chaetomium globusum, Chalara, Hypoxylon*, *Phoma,* and *Xylaria.* Three novel cytochalasins including; epoxycytochalasin H, cytochalasin H, cytochalasin J and known compound cytochalasin E have been reported from a *Rhinocladiella* sp. isolated from *Tripterygium wilfordii* [18]. Anticancer agent, vincristine has been collected from mycelia sterilia, inhibiting *Catharanthus roseus* and also induced antitumor activity [19].

Potential of entophytes have received great attention due to the fact that, endophytic fungi have been shown to be a promising source of bioactive compounds bearing pharmaceutical, and there is an indication that these fungi contain bioactive compounds that mainly kill cancer cells by apoptosis. Also, endophytic fungi as a promising alternative units in myco synthesizing these nanoparticles with an improved application for prospective future drugs. The endophytes isolated from various plants was used to fabricate nano particles and nanomaterials [20]. Recently, nano-chemotherapy has provided effective delivery systems for docetaxel drug, which can increase its water solubility, reduce the risk of side effects and increase the cancer-targeting dissemination by passive or active targeting drug delivery [21].The relation between endophytic microbes and develop a novel nanomaterials is a relatively innovative and unexplored area and may open possibilities in the future to push the frontier forward in forthcoming years. Additional studies are required to discover more antitumor agent and develop more efficient nanoformulations for prospective future for anticancer agents by hidden fungi.

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